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Polymeric nanoparticles – Influence of the glass transition temperature on drug release

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ABSTRACT

The physico-chemical characterisation of nanoparticles is often lacking the determination of the glass transition temperature, a well-known parameter for the pure polymer carrier. In the present study the influence of water on the glass transition temperature of poly (DL-lactic-co-glycolic acid) nanoparticles was assessed. In addition, flurbiprofen and *m*THPP as model drugs were incorporated in poly (DL-lactic-co-glycolic acid), poly (DL-lactic acid), and poly (L-lactic acid) nanoparticles. For flurbiprofen-loaded nanoparticles a decrease in the glass transition temperature was observed while *m*THPP exerted no influence on this parameter.

Based on this observation, the release behaviour of the drug-loaded nanoparticles was investigated at different temperatures. For all preparations an initial burst release was measured that could be attributed to the drug adsorbed to the large nanoparticle surface. At temperatures above the glass transition temperature an instant drug release of the nanoparticles was observed, while at lower temperatures less drug was released. It could be shown that the glass transition temperature of drug loaded nanoparticles in suspension more than the corresponding temperature of the pure polymer is the pivotal parameter when characterising a nanostructured drug delivery system.

1. Introduction

The encapsulation of drugs into colloidal systems has become a very popular method to achieve drug targeting and enhance drug efficiency (Torchilin, 2007). Polymer based nanoparticles are a prominent representative of colloidal systems besides liposomes and drug-polymer conjugates (Petros and DeSimone, 2010). Different natural or synthetic materials are used for nanoparticle preparation. Especially poly (lactic acid) (PLA) and its copolymer with glycolic acid, poly (DL-lactic-co-glycolic acid) (PLGA), are commonly used for particle preparation due their distinct biodegradability and biocompatibility (Alexis, 2005).

The characterisation of such colloidal systems most often includes the determination of particle diameter and size distribution via dynamic light scattering as well as further analytics concerning the morphology, i.e. scanning electron microscopy (SEM). Additionally, in many cases the determination of surface charge is performed in order to estimate colloidal stability and aggregation tendency (Peltonen and Hirvonen, 2008). However, the determination of the glass transition temperature (Tg) of nanoparticles in aqueous dispersion is less established, although Tg represents an important parameter of the pure polymer carrier. In most cases when Tg of the resulting polymeric nanoparticle system is quantified, a solid sample is analysed with the focus on the physical state of the embedded drug in terms of drug crystallisation or the formation of a solid solution (Dillen et al., 2004; Pamujula et al., 2004; Sant et al., 2005). Nevertheless, the relevance of Tg in aqueous nanoparticle dispersions is often underestimated. Especially for drug-loaded nanoparticles where a drug substance is incorporated in a polymeric matrix there are manifold interactions between the polymer chains and the drug due to their physical closeness.

Another characteristic of drug-loaded polymeric nanoparticles is the release profile. There are several factors that may influence drug release from the nanoparticulate system, e.g. drug solubility, diffusion, polymer biodegradation, particle size, and drug loading. For instance, there is a direct correlation between drug loading and initial burst release as well as subsequent release rate of the encapsulated amount (Kumari et al., 2010). Furthermore, the effect of different emulsifiers or steric stabilisers used in various concentrations for particle preparation also contributes to the release profile. For example the use of 0.5% instead of 5% poly (vinyl alcohol) (PVA) during nanoparticle preparation leads to an

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increased release of encapsulated bovine serum albumin (BSA) (Sahoo et al., 2002). Furthermore, the liberation of paclitaxel from PLGA nanoparticles is decreased when using 1,2-dipalmitoylphosphatidylcholin (DPPC) as an emulsifier instead of PVA (Feng and Huang, 2001). In addition, Budhian et al. described that the ratio of lactic to glycolic acid in the polymeric matrix additionally affects the burst release from haloperidol-loaded PLGA nanoparticles (Budhian et al., 2008). Moreover, other authors addressed the influences of the release medium on drug release from PLGA microspheres (Faisant et al., 2006). The release of 5-fluorouracil is strongly dependent on the osmolarity, buffer concentration, pH value, and temperature of the chosen incubation medium. However, when considering these studies a correlation between Tg of drug-loaded nanoparticles and temperature dependent release behaviour is not described so far.

The present study is focussed on a relationship between Tg influencing parameters and release profile kinetics. Glass transition temperatures of unloaded PLGA nanoparticles in dry form and in aqueous suspension were examined to reveal possible effects of the used emulsifier and stabilisers. In a second step, drug-loaded PLGA nanoparticles were characterised for drug loading, Tg, and physical state of the incorporated model drugs flurbiprofen and 5,10,15,20-tetra(*m*-hydroxyphenyl)porphyrin (*m*THPP) (Fig. 1). Both drugs were chosen because of their poor water solubility in combination with an insufficient transport across biological barriers which necessitates suitable drug formulation strategies such as the incorporation in colloidal dosage forms (Meister et al., 2013; Grünebaum et al., 2015).The release behaviour of the model drugs from PLGA nanoparticles was compared to nanoparticles based on DL-PLA and L-PLA, in order to compare typical biodegradable and approved starting materials for nanoparticle preparation. By using different temperature profiles the release behaviour could be correlated to Tg properties of the respective nanoparticle formulation.

2. Materials and methods

2.1. Materials

PLGA (Resomer® RG502H, inherent viscosity 0.16–0.24 dl/g), DL-PLA (Resomer® R203H, inherent viscosity 0.25–0.35 dl/g), and L-PLA (Resomer® L206S, inherent visosity 0.8–1.2 dl/g) were obtained from Evonik Industries AG (Darmstadt, Germany). *m*THPP was kindly provided from biolitec research GmbH (Jena, Germany). Flurbiprofen (FBP), human serum albumin (HSA), poly (vinyl alcohol) (PVA), and mannitol were purchased from Sigma Aldrich (Steinheim, Germany). The purity of the drugs was ≥98.5% according to the specifications of the suppliers. All other reagents were of analytical grade and used as received.

2.2. Nanoparticle preparation

For nanoparticle preparation an emulsion diffusion method was used. To obtain unloaded PLGA nanoparticles 125 mg of the polymer was dissolved in 2.5 mL ethyl acetate and 5 mL of an aqueous solution containing 1% (w/v) PVA was added. After homogenisation at 15,000 rpm for 5 min (Ultra Turrax®, S25NK-19G, IKA, Staufen, Germany), the emulsion was diluted with 7.5 mL 1% (w/v) PVA solution. After evaporation of ethyl acetate by stirring the emulsion over night at room temperature, the nanoparticles were washed once by centrifugation and redispersion in purified water.

For drug-loaded PLGA nanoparticles 100 mg polymer and 2.5, 5, 10, 20, and 30 mg flurbiprofen, respectively, or 10 mg *m*THPP were dissolved in 1 mL ethyl acetate. After addition of 2 mL of 1% (w/v) PVA solution, this mixture was homogenised under cooling for 30 min at 24,000 rpm (Ultra Turrax®, S25N-10G, IKA, Staufen, Germany). The emulsion was subsequently diluted with 8 mL 1% (w/v) PVA solution. The removal of the organic solvent and purification was performed as described for unloaded PLGA-NP.

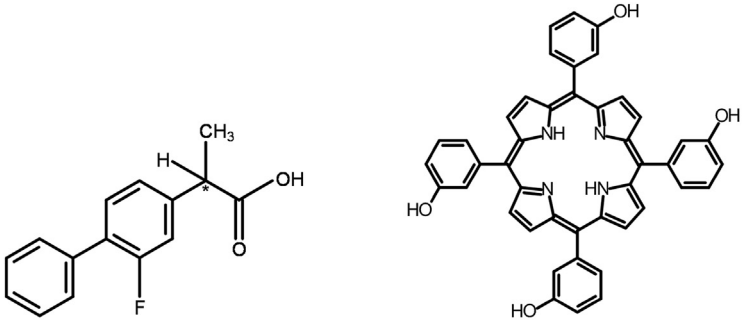
The preparation of DL-PLA and L-PLA nanoparticles was carried out using a solution of 100 mg polymer and, in the case of flurbiprofen-loaded nanoparticles, 10 mg flurbiprofen in 2 mL methylene chloride. For *m*THPP-loaded PLA nanoparticles 10 mg drug and polymer were dissolved in a mixture of 1 mL ethyl acetate and 1 mL methylene chloride, respectively. The addition of 6 mL 1% (w/v) PVA solution was followed by homogenisation under cooling for 30 min at 24,000 rpm (Ultra Turrax®, S25NK-19G, IKA, Staufen, Germany) and subsequent dilution with another 6 mL 1% (w/v) PVA solution. Further solvent removal and purification was performed as described before.

2.3. Lyophilisation and reduction of residual moisture

All prepared nanoparticle suspensions were freeze dried in the presence of mannitol using a single chamber-system (Epsilon 2–4, Martin Christ, Osterode am Harz, Germany).

For unloaded PLGA-NP a concentration of 10% (w/v) mannitol was added to the samples. The freeze drying process was performed as follows: Freezing at −40 °C for 7 h, a primary drying step at −34 °C and a vacuum of 0.05 mbar for 40 h, followed by a secondary drying phase at 20 °C and 0.025 mbar for 11 h. Further extraction of residual water in the freeze dried product was achieved by storage in a desiccator at an elevated temperature of 40 °C for 2–72 h.

For flurbiprofen-loaded PLGA nanoparticles mannitol was used in a reduced concentration of 3% (w/v) to enable DSC analysis of the drug in the particle samples. The freeze drying process was



Flurbiprofen 5,10,15,20-tetra(*m*-hydroxyphenyl)porphyrin (*m*THPP)

Fig. 1. Molecular structure of the drugs flurbiprofen and 5,10,15,20-tetra(*m*-hydroxyphenyl)porphyrin (*m*THPP).